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CURRENT ISSUES IN VACCINATION
Steven Holloway BVSc, MVS, DACVIM, PhD
Department of Veterinary Clinical Sciences
The University of Melbourne
Princes Highway, Werribee, Vic. 3030

Dogs
Issue 1. Duration of Immunity and Annual Vaccination in Dogs

There is now considerable evidence that yearly vaccination against CDV, CPV and CAV-1 is not required. Studies have shown that immunity to all 5 antigens is maintained for periods of over 2 years and for CDV, CPV2, CAV, CPiV for over 4 years. The weight of evidence suggests that we are able to vaccinate less often in dogs, probably every 3 years for core viruses and probably at least 2 yearly for respiratory vaccines. Duration of immunity studies overwhelmingly support that dogs over 1 year of age are protected for periods of over 3 years and maybe a lot longer. In other words it is not possible to defend the practice of annual vaccination for CPV2, CDV, CAV given the volume of data available. Secondly, the duration of immunity of Bordetella vaccines is not 3 years and the longest duration of immunity published is less than 2 years and so yearly Bordetella vaccination is still necessary until products with longer duration of immunity are registered for use. Parainfluenza virus vaccines appear to give 2-3 years duration of immunity based upon present studies. As neither of these agents would usually cause fatal disease then a decision of whether to vaccinate yearly against these agents should be made after a consultation with the dog’s owners. Such a discussion would take into account the dogs access to other dogs and possible kennelling requirements where the risk of exposure is higher.

Many veterinarians would say “So why not just vaccinate against all 5 antigens yearly if they do no harm”? Or “Basing our policies on DOI data is too difficult”.

Issue 2. Are Vaccines Safe?

A major concern of the repeated use of vaccines is the potential to develop serious immune-mediated diseases following vaccines. Surprisingly, little has been published on the incidence of immune-mediated diseases after vaccination. Idiopathic immune-mediated haemolytic anaemia (IMHA) was identified in a retrospective, controlled study of 58 dogs over a 27-month period. When compared with a randomly selected control group of 70 dogs (presented for reasons other than IMHA) over the same period, the distribution of cases versus time since vaccination was different (P < .05). Fifteen of the dogs (26%) had been vaccinated within one month of developing IMHA (P < .0001), whereas in the control group no marked increase in the frequency of disease was seen in the first month after vaccination. The recently vaccinated dogs with IMHA (vaccine IMHA group) had significantly lower platelet counts (P < .05) and a trend towards increased prevalence of intravascular haemolysis and autoagglutination when compared with the non-vaccine IMHA group. In the recently vaccinated dogs, combination vaccines from various manufacturers against CDV, CAV-2,
leptospirosis, parainfluenza, and CPV-2a (DHLPP) were involved in each case. Vaccines against rabies virus, Bordetella spp, coronavirus, and Lyme Borrelia bacterins were administered concomitantly to some dogs. This study provides the only clinical evidence for a temporal relationship of vaccine-associated IMHA in the dog. Clearly, better reporting of potential vaccine related immune-mediated disease is required and veterinarians assessing cases of IMHA should be active in reporting possible relationships to vaccination.

A more recent study was conducted to evaluate the safety of canine vaccines. An epidemiological investigation was conducted to evaluate the evidence for a temporal association between vaccination and ill health in dogs. The owners of a randomly selected population of dogs were sent 9055 postal questionnaires, 4040 of which were returned. No temporal association was found between vaccination and ill health in dogs after adjusting for potential confounders, such as age. However, reliable inferences from non-significant test results are limited and so equivalence-testing methods were also used to make informative inferences. Results demonstrated that recent vaccination (<3 months) does not increase signs of ill health by more than 0.5% and may actually decrease it by as much as 5%. This general approach to questions of vaccine related disease should be used in all field studies of vaccine safety. Conditions and do not spread to other dogs. However, encephalitis has very occasionally been reported after vaccination with modified-live CDV vaccines. This is most likely to occur with the vaccination of bitches in whelp or during the first few days post-partum. Clinical signs are usually restricted to jaw champing fits and resolution has been reported. The detection of CDV RNA within the bone cells of dogs with metaphyseal osteopathy (hypertrophic osteodystrophy) has led to the suggestion that CDV may be the cause of the disease in large breed young growing dogs. These conflicting findings suggest that infection of metaphyseal bone cells is common in young dogs with systemic wild type distemper and occurrence of viral antigen in these cells may result in defects in bone modelling. There is at present no direct evidence of vaccine virus causing metaphyseal osteopathy in dogs, although the possibility cannot be excluded. It might be added that should vaccinal CDV be implicated in the development of these diseases then the use of alternatives vaccines to MLV CDV vaccines might be appropriate. In such a situation, CDV containing canarypox vaccines may be the preferred option. A special note needs to be stated concerning Weimaraners. Weimaraners appear to be at increased risk of developing metaphyseal osteopathy following vaccination and there is at least some evidence suggesting that breaking up the vaccination interval may result in less chance of developing HOD. It is important to remember that not all dogs in the population will behave identically and in some cases certain individuals may have a predisposition to hyper or hypo immune responsiveness to infectious agents or adjuvants used in vaccines.

Should we vaccinate against Leptospirosis?

It is important for practitioner to realise that Leptospira interrogans is a species containing multiple different serogroups containing multiple serovars. Each
serogroup contains several serovars that are closely related due to their antigenic determinants on the outer membrane. These outer membrane antigens are responsible for the induction of agglutinating antibodies in infected animals and are the basis of the in vitro phenotypic classification of leptospires by the micro agglutination test. More recently a classification system based on DNA identification is in use and the previously unique species *L. interrogans* is subdivided into and least seven genomospecies. The different classification systems have provided confusion for field veterinarians. The numerous serogroups may have variation in virulence for dogs also and certain serovars are more often associated with clinical leptospirosis than others. For example common serogroups causing clinical disease in dogs include *icterohaemorrhagiae, canicola, sejroë, australis, grippotyphosa and autumnalis*. *Icterohaemorrhagiae and canicola* are traditional serogroups associated with canine leptospirosis but other serogroups can also cause disease in dogs. Dogs are the natural host of canicola and rats *icterohaemorrhagica*. These two serogroups are most commonly included in vaccinations. Leptospirosis may therefore be affected by the prevalence of rodents or infected dogs in the environment and also environmental conditions such as the availability of temperate fresh waters such as lakes and streams\(^{14}\). In dry areas, the disease would appear to have a lower incidence making vaccination less necessary.

In my opinion, Australian studies have been inadequate to assess virulence, serovar prevalence of clinical signs related to infection. This has recently improved with a study suggesting that leptospirosis is a serious problem in dogs in Northern Queensland\(^{15}\) with *L. australis* (80%) and *L. zanoni* (15%) with individual cases of *L. hardjo* and *L. copenhageni* reported. Key issues then relate to the serovars in Australian vaccines and cross protection against those found in North Queensland occur. Similar questions need to be asked in each locality then to determine if vaccination is required or even effective. To assess vaccine effectiveness challenge studies are usually undertaken and these studies often show that challenge with other serogroups are usually less effective in protecting against chronic disease and renal carriage than the vaccinal serogroup \(^{16}\). Newer strategies to increase the concentration of potentially cross protective protein antigens especially those expressed during infection may improve cross protection. Vaccine manufacturers may need to update include some of the more relevant serovars to guarantee protection.

**Should we vaccinate against canine coronavirus**

An effective coronavirus vaccine is one that induces and maintains significant concentrations of virus-specific antibodies in serum and at local points of viral entry (e.g., mucosal surfaces), as well as virus-specific T-cell immunity. A strong neutralizing antibody response and a specific mucosal antibody response are therefore desirable. Canine Coronavirus (CCoV) and feline corona viruses (FeCoV) are group I corona viruses with a predominantly enteric replication pattern. CCoV, FeCoVs are divided into type I and type II serotypes. By sequence analysis and comparison, it has been demonstrated that two prototype
strains of FeCoV type II originated from double and separate recombination events between FeCoV type I and CCoV 2. As FeCoV II has an S protein derived from CCoV they are serologically cross-reactive. There is no doubt that CCoV show levels of nucleotide and antigenic variability. In fact, several studies demonstrate variance of Australian and European isolates from the prototypical sequences of CCoV. A major problem when determining if any particular vaccine will produce immunity against any particular challenge virus is an understanding of the host immune response and the relationship to the circulating virus type in the local area where the vaccine will be used. This can be addressed easily for some viruses but is problematic for many. For example, canine parvovirus 2 (CPV2) is a relatively well-studied virus and neutralization epitopes of the virus have been well documented. Despite antigenic and nucleotide variation, current CPV2 vaccines produce serum antibodies to conserved neutralization epitopes. By comparison with CPV2, CCoV is a much larger virus, shows greater nucleotide and antigenic variation and the documentation of important protective epitopes (both antibody and CTL) have not been documented for any CCoV type. As such, any argument for vaccination (pro or con) based on molecular analysis of circulating types of CCoV is likely to be deficient until we know specific areas of the virus that stimulate protective immunity. CCoVs appear to be of variable pathogenicity with various reports suggesting mild disease to severe or fatal disease. At present the utility of CCoV vaccination is therefore debatable.

Cats

Issue 1. Duration of Immunity

Herpesvirus FHV-1 and Calicivirus (FCV) and FPV. In cats current evidence suggests that vaccination of kittens and boostering at 1 year of age will provide long lasting immunity against FPV. With FCV issues of strain variation will cloud whether vaccination is helpful at all. However, in studies relating FCV antibody titres to challenge with virulent virus there was a good correlation with antibody titres and protection from disease. Most cats (>90%) would seem to have protective titres at three years and so a 3-yearly vaccination interval would seem appropriate. FHV remains the most difficult virus to make recommendations for. Antibody titres have a good correlation with protection against challenge in 90% of cats but duration of immunity may not be greater than 3 years. Additionally, the effects of stress on reactivation of latent herpesvirus infections is unknown despite antibody titres that would appear adequate. (This is why genital herpes is such a difficult issue in human medicine!) Whether vaccination provides enough cell-mediated immunity to prevent this stress reactivation is also an issue. For FHV a clear answer on how often to vaccinate is impossible at present and even the effectiveness of vaccination in the prevention of stress related shedding and disease is hard to evaluate. In Scott’s study vaccinated cats were protected partially against viral challenge with virulent FHV three years after vaccination. Relative efficacy of the vaccine, on the basis of reduction of clinical signs of disease, was 52%. This
would suggest that there is some immunity carried through to 3 years. Would it stand up in a high challenge environment?

**Issue 2: FIV vaccines**

Obviously FIV is a big problem in Australia, with many cats being infected. In one study seroprevalence rates are >20% of cats in the inner city. The virus clearly has correlation with diseases in cats particularly lymphosarcoma and so a vaccine is indicated. Is the current FIV vaccine efficacious? The vaccine is a killed vaccine and contains two isolates of the virus one from Clade A and one from Clade D (subtype A FIV (Petaluma) and subtype D FIV (Shizuoka) vaccine. At present all Australian isolates have been suggested to be Clade A. Previous challenge studies in vaccinated cats indicate broad protection against multiple strain of the FIV virus and the preventable fraction is around 82%. However, no killed vaccine has protected against the highly virulent Glasgow strain. We can therefore expect perhaps that not all vaccinated cats will be protected but that vaccination may over time reduce the prevalence of FIV. Successful protection in any one cat may depend upon the age at which the cat is challenged, and the virulence of the challenge virus more than the antigenic type. A downside to the vaccine is that it renders cats’ antibody positive and so serological discrimination of virus positive cats is not possible in vaccinated cats. Therefore it would seem logical to test cats prior to vaccination. However be aware that maternal antibodies will carry over in kittens born of vaccinated queens and positive kittens will require further testing to see if this is true infection or not. In the USA considerable variation has been found with different laboratories conducting FIV testing suggesting that PCR may have issues with accuracy. A high number of false-negative test results when using polymerase chain reaction-based assays. A recent study showed a PCR-based assay was false negative on one of 10 tests for subtype A and one of 12 for subtype B. In general, the PCR assay is a wonderful tool, but concern about its current usability as a commercial diagnostic test for FIV exists.

**Feline Calicivirus**

Highly virulent forms of feline calicivirus (VS-FCV) have emerged that cause a severe systemic infection may be fatal. Currently, there are no genetic or in vitro diagnostic methods to distinguish viruses isolated from cases of VS-FCV disease from other isolates. Infected cats that recover from acute disease remain persistently infected. In such cats, continuing viral mutation enables the virus to evade the host immune response and long-term carriers may enable the virus to persist in the feline population. FCV vaccines have been available for many years and in general they reduced the incidence of clinical disease without providing sterilising immunity. Vaccinated cats can still become persistently infected and shed virus. In addition, FCV strain variability my result in variable protection after vaccination. The emergence of more virulent FCV and ongoing
evolution of the virus may necessitate the development of new vaccines for FCV.

Do viral vaccines made in feline kidney cells induce renal disease?

In theory, vaccine viruses grown in feline kidney cells could result in immune-mediated kidney disease in vaccinated cats. If sufficient cellular material from the kidney cell line (CRFKs) is carried forward in the presence of adjuvants then in theory the tolerance to self-antigens may be overcome and auto reactive antibodies produced. Two recent papers by Lappin et al suggest that this may occur in cats although the link to interstitial nephritis is still not supported by studies in a large number of cats. In a 2006 study by Lappin et al, parenteral administration of CRFK cell lysates or FHV 1, FCV, and FPV virus-containing vaccines (FVRCP) grown on CRFK cells induced antibodies against CRFK cells. These antibodies also react with feline renal cell extracts. This paper suggests the possibility may of vaccine-induced renal disease. In a second study, interstitial nephritis was detected in cats that were immunologically sensitised with CRFK lysates, boosted with CRFK lysates, and then biopsied 2 weeks after the booster (13 injections in all). One cat in each of the three CRFK lysate sensitisation groups had lymphocytic-plasmacytic interstitial nephritis. Although not conclusive this paper raises questions of a link between feline interstitial nephritis and repeated vaccinations with killed, feline viral vaccines produced in CRFKs.

References

Available on request from stevenah@unimelb.edu.au